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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/529,951

04/01/2005

Peter John Barton

ASZD-P01-863

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ROPES & GRAY LLP

PATENT DOCKETING 39/41

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EXAMINER

CHANG, CELIA C

ART UNIT

PAPER NUMBER

1625

MAIL DATE

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02/04/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

Application No.

10/529,951

Applicant(s)

BARTON ET AL.

Examiner

Celia Chang

Art Unit

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 21 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 10,11,13 and 22-25 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 10,11,13,22-25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

1. Applicant's election of Group I, claims 10-11, 13 in the reply filed on Nov. 21, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 10-11, 13 and the newly added claims 22-25 are pending.

2. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The scope of the claim is ambiguous and confusing because the compounds being provisoed out is not within the Markush elements. specifically, Y does not include pyridinyl yet the provisoed compounds Y is pyridinyl. Clarification is required.

3. Claims 10-11, 13, 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the

evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the *In re Wands*, 8 USPQ 2<sup>nd</sup> 1400 (1988) decision.

The analysis is applied to the instant case.

*Nature of invention and the breadth of the claims*

The claims are drawn to a group of Markush compounds which possess the activity of human 11-13-hydroxysteroid dehydrogenase type 1 enzyme (11 $\beta$ HSD1) inhibitory activity, and accordingly have value in the treatment of diseases. The scope of the claims encompassed enormous structurally diverse compounds with multiple utility in treating all disorders from diabetes, obesity, hyperlipidemia etc. which is extremely broad.

*The state of the art and predictability*

Enzyme inhibition is extremely structural sensitive. Compounds that inhibit enzyme requires very specific size, configuration and electrical charge. It is very much like a lock and key situation, the key being the claimed compounds. The biological systems are capable of distinguishing between enantiomers of any different compounds. In general just one of the enantiomers produce the characteristic effect, the other enantiomer produces no effect or has a totally different effect. For example, the R-enantiomer quinidine has cardiac effect, while the S-enantiomer Quinine has anti-malarial effect.

There is very little known about mechanisms of how modification in binding compounds structurally would the enzyme 11-13-hydroxysteroid dehydrogenase type 1 enzyme (11 $\beta$ HSD1) activity be affected thus resulting in pharmacological intervention. However, compounds that falls within the broad Markush description have been evidenced to have drastically diverse utility when small changes in the structure occur. Specifically, it is noted that when the instant Y is pyridinyl, the compounds have serotonin antagonistic activity (see CA 106:213767); when Y is di-hydroxy substituted phenyl, the compounds are glutaminergic transmitter agonist (See CA 113:77921); when (R<sup>1</sup>)<sub>n</sub> is 2,5-difluoro, the compounds have muscarinic receptor stimulating activity (see CA 141:207058). State of the art indicated that small difference in chemical structure will result in diversified utility.

*The amount of guidance and working examples*

The specification provided, *in vitro* enzyme inhibition data on three compounds (see p.54). All three compounds are (R<sup>1</sup>)<sub>n</sub> is 4-OMe or 4-OCF<sub>3</sub>; Y is 4-F or 4-OCF<sub>3</sub> phenyl. In view of the scope of the claims broadly encompassed enormous number of substituents at variable positions with an ambiguous scope of what Y is, such exclusive di-4-substituted phenyl compounds cannot provide sufficient support that all the claimed compounds having the same 11 $\beta$ SD1 enzyme activity. No where in the specification or prior art that an activity-structural relationship for the enzyme justify the extrapolation of the data from three limited structure to the scope of the claims. *In re Fisher* 166 USPQ 18, indicated that the more unpredictable the field of activity, the more enablement by way of specific examples is necessary in order to establish the broad scope of the claims. In view of the factual evidence noted in the state of the art as clearly delineated supra, the specification thus, failed to provide those having ordinary skill

in the art reasonable assurance as by adequate representative examples that myriad of compounds falling within the scope of the claims all will have efficacy in 11 $\beta$ HD1 activity.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 11 is provisionally rejected under 35 U.S.C. 102(e) as being anticipated by US 2005/0124627.

Schadt et al. '627 disclosed anticipatory compound when Y is optionally unsubstituted phenyl and R1 is 4-fluoro (see 16, compound 9) Sugimoto et al. US 4,990,511. Schadt et al. '627 has an effective filing date of Mar. 5, 2003 and entitled to the priority date of Mar. 12, 2002 which is prior to the instant priority date.

Since Schadt et al. '627 has not yet been patented and the granting of priority benefit has not been issued, a provisional rejection is made.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sugimoto et al. JP 61-227565 supplemented with CA 106:213767.

The 8<sup>th</sup> compound of claim 10 is chloro-substituted while the prior art exemplified a fluoro substituted species (see RN 107025-74-1). Generically, Sugimoto et al. '565 taught that Markush elements selected among all halogens are optional choices for such substitution (see col. 1-2 formula I). In absence of unexpected results, there is nothing unobvious in choosing some among many. In re Lemin 141 USPQ 184.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 11, 13, 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakajima et al. US 4,990,511 supplemented with CA 113:77921.

Nakajima et al. '511 disclosed the compound being provisoed out by claim 11 (see 10th proviso). Proviso, although disclaimed the exemplified species, does not exclude the generic variation as taught by the reference wherein Markush elements selected among all halogen and positions are optional choices for such compounds (see col. 1-2 description for formula). In

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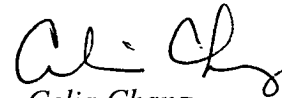
absence of unexpected results, there is nothing unobvious in choosing some among many. In re Lemin 141 USPQ 184.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang  
Jan. 31, 2008

  
Celia Chang  
Primary Examiner  
Art Unit 1625